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Risk of cytomegalovirus transmission by blood products after solid organ transplantation

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ABSTRACT

Cytomegalovirus (CMV) infection and CMV disease are significant contributors to increased morbidity, mortality, and cost for immunocompromised solid organ transplant recipients. Although the most significant risk for CMV transmission is the CMV serological status of the transplant donor and recipient, exposure to blood products is another potential risk factor. Before the era of leukocyte reduction, CMV seronegative products were issued to reduce the risk of CMV transmission, thus rendering the products CMV safe. This approach requires maintenance of two inventories of blood products and continuous donor testing. Leukocyte-reduced cellular transfusion products are also considered CMV safe and are essentially universally available. To minimize the risk of CMV infection in transplant recipients, strategies include use of seronegative blood products or prestorage leukocyte reduction. However, no recent randomized prospective controlled trial directly compares the two CMV safety approaches for transplant recipients. Hence, current policy relies on historic trials and more recent observational studies. As a consequence, though generally considered equivalent approaches, preferred practice varies between centers. This review provides guidance to inform an acceptable practice approach.

KEYWORDS CMV safe; CMV seronegative; cytomegalovirus; leukocyte reduction; solid organ transplantation; transfusion

Human cytomegalovirus (CMV), a leukocyte-associated beta-herpes virus, remains a significant cause of allograft failure, morbidity, and mortality in solid organ transplant (SOT) recipients.[1,2] The typical disease transmission route is from a CMV positive organ into a CMV negative recipient. However, before leukocyte reduction of blood products, blood transfusion–transmitted CMV (TT-CMV) was also a known CMV transmission risk. Although not eliminated, the risk was mitigated by using blood products collected from CMV seronegative blood donors, rendering these products CMV safe. In the current era, essentially all cellular blood products are leukocyte reduced using third or fourth-generation filter technology, substantially removing the potentially infectious white blood cells and, thus, are also considered CMV safe. The question often arises about the advantages of one approach over the other. To address the question of using leukocyte reduction vs identifying CMV seronegative blood products, each approach and pertinent literature is reviewed to discern a reasonable recommendation.

CMV INFECTION AND DISEASE

CMV is endemic throughout the world. In the USA, CMV seroprevalence rates range from 30% to 97%.[2–4] As a consequence, most of the blood supply is derived from CMV exposed and mostly seropositive donors. Primary CMV infection may present as an acute upper respiratory infection, but more frequently is subclinical with few overt symptoms. Resolution of primary viremia occurs with the emergence of antibodies. Once the infection is cleared, CMV resides within blood leukocytes and progresses to a latent phase. Either secondary infection with a variant strain of CMV or reactivation may occur causing secondary viremia. In healthy individuals, primary and reactivation infections are of little consequence. However, immune-deficient individuals can experience severe or even fatal disseminated infections. During the carrier or latent phase of CMV infection, the donor is asymptomatic and fulfills requirements to donate blood. To be clear, CMV infection and disease are not synonymous terms, and all infected patients do not develop overt clinical disease. Infection represents the isolation of

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viral proteins or nucleic acid in any body fluid or tissue regardless of symptoms or signs. Disease is characterized by infection with attributable signs and symptoms (i.e., fever, malaise, leukopenia, neutropenia) and evidence of tissue-invasive disease (i.e., pneumonitis, retinitis, hepatitis).

Given the potentially devastating consequences of CMV disease for SOT recipients and the known risk of transplanting a CMV positive organ into a CMV negative recipient, transplantation services have developed pharmacological and laboratory approaches typically based upon risk stratification to mitigate risk.[5–7] The stratification approach assigns risk based upon donor and recipient CMV serological status. For example, CMV positive donor/CMV negative recipient (D+/R−) is designated the highest risk for CMV transmission. Moderate risk is assigned to CMV positive recipients irrespective of donor status (D±/R+). The CMV negative donor/CMV negative recipient (D−/R−) population is considered low risk. Once patients are stratified by CMV risk category, the clinical approach to CMV risk mitigation may use either universal prophylaxis with antiviral agents (i.e., ganciclovir, valganciclovir) or continuous sensitive laboratory CMV monitoring to detect viral antigenemia, which is termed the preemptive approach. Because each approach is acceptable, practice varies by institution.

APPROACHES FOR TRANSPLANT RECIPIENTS

Antiviral prophylaxis (i.e., oral valganciclovir, ganciclovir) is typically used for 3 to 6 months posttransplantation to prevent CMV infection and disease in D+/R− patients. This strategy decreases the incidence of initial allograft rejection and opportunistic infections. However, it is associated with late-onset CMV disease, which occurs after discontinuation of prophylaxis.[2] Universal prophylaxis also has the potential for toxicity and the emergence of drug-resistant strains.

The other approach is preemptive therapy. The concept is to identify CMV infection while the disease is asymptomatic. This approach relies on intensive weekly laboratory surveillance, typically using sensitive nucleic acid testing assays for at least 12 weeks posttransplantation. Treatment is not instituted until the virus is detected. This approach significantly reduces CMV disease and its delayed onset. However, it can be difficult to coordinate and is associated with higher laboratory costs.[5] Regardless of the antiviral prevention approach used, it is worth noting that most SOT patients today are receiving either antiviral treatment or are being monitored for the presence of CMV emergence. Hence, the a priori transfusion-transmission risk leading to CMV disease is lower than in previous decades.[8]

APPROACHES FOR BLOOD BANKS

Along with advances in the medical prophylactic treatment and preemptive mitigation of CMV disease, blood banks have adopted approaches to render products *CMV safe*. CMV safe can be confusing terminology. The term generally refers to the fact that a CMV reduction strategy was applied to the blood product. Current and commonly available strategies to reduce TT-CMV risk include either selecting only CMV seronegative blood products (termed CMV seronegative) for transfusion therapy or performing leukocyte reduction.

In the 1990s, serological testing of blood donors was performed using various methodologies, including latex agglutination (sensitivity 93%, specificity 100%), indirect hemagglutination assay (sensitivity 89%, specificity 90%), and enzyme immunoassay (sensitivity 93%, specificity 95%). Currently, the systems that are approved by the US Food and Drug Administration (FDA) include Capture-CMV®, a solid-phase red cell–adherence test with relative sensitivity of 99.2% to 100% and relative specificity of 98.9% to 100%, and Olympus® PK™ CMV-PA, a passive particle agglutination test with a specificity of 99.3%. The purpose of the testing is to identify immunoglobulin (Ig) G or total (IgG, IgM) CMV antibodies. If absent, the blood product could be labeled CMV serologically negative. As simple as that algorithm appears, the various methodologies cited have such a range of sensitivities and specificities that a percentage of CMV negative declarations will in fact be false-negative results.[9] Second, the window phase for CMV appears to be at least several weeks. Hence, seronegative donors can be CMV viremic and potentially infectious. This risk is compounded by the fact that CMV-infected blood donors are often asymptomatic. In addition, contrary to conventional wisdom, recent studies have demonstrated that viremia and the presence of detectable IgG antibody may coexist in the early phase of the infection.[10] Hence, it must be clearly understood that being labeled CMV seronegative and/or referred to colloquially as CMV negative is not a guarantee that a blood product is CMV viral negative with no possibility of transmitting CMV.

A common alternative approach to create a CMV safe blood product is leukocyte reduction. By definition, leukocyte reduction means that a blood product should have fewer than 5×10^6 leukocytes per unit. Several methodologies can achieve leukocyte reduction. First, leukocytes can be removed via filtration. Today, third and fourth-generation filters (either nonwoven depth or woven screen filters) are used. These filters, which are made from polyesters and take advantage of the negative electrostatic charge of leukocytes, achieve at least a 99.9% or 3-log reduction of leukocytes.[11] Before the current era, leukocyte filtration was often performed at the patient's bedside. After a non–leukocyte reduced unit of blood was issued, transfusion staff would use a blood administration kit that included a leukocyte reduction filter between the unit of blood and the recipient. Considered to yield inconsistent leukocyte reduction results,[12] today that practice has been superseded. Most whole blood collected today is leukocyte reduced via an in-line filter—a procedure performed in blood component laboratories shortly after collection. Apheresis achieves similar results by separating cell fractions (i.e., plasma, buffy coat, red blood cells) via centrifugation, which takes advantage of the differential specific gravity of each fraction. As the fractions separate, the buffy coat is selectively removed, eliminating most of the leukocyte fraction from the blood component.

Other approaches include either washing red cell units and removing the buffy coat or manipulating the blood product via glycerolizing, freezing, thawing, and subsequent deglycerolizing. Although both of these methods reduce the risk of CMV transmission, neither is practical on a large scale, and both are associated with increased cost. In addition, manipulating the blood product via glycerolizing, freezing, thawing, and deglycerolizing has been associated with acidosis in an infant.[9] Finally, the risk reduction from washing cellular blood products and removing the buffy coat is insufficient to consider the product CMV safe.

EFFICACY OF BLOOD BANK APPROACHES

Although current leukocyte reduction and CMV serological testing as CMV blood product prevention strategies have not been compared in a multicenter, prospective, blinded, randomized clinical trial to test for either superiority or, at least, noninferiority, a fair number of good studies have been published. Understanding this literature requires awareness that studies performed over the decades may not be comparable given developments in clinical practice, pharmacological approaches to prevention and treatment of CMV, and blood bank technology.

Before TT-CMV reduction strategies, the risk of CMV infection for seronegative marrow recipients ranged from 28% to 57%.[13] With the introduction in the late 1980s of selecting only CMV seronegative blood products for high-risk populations, the risk of CMV infection declined to <5% (varying from 1% to 4%, depending upon the study). Hence, CMV seronegative blood products became the de facto standard of care for prospective immunocompromised transfusion recipients who were not previously exposed to CMV. In the mid-1990s, to study leukocyte reduction as an alternative CMV reduction strategy, Bowden and coauthors[14] conducted a prospective randomized trial comparing the use of bedside leukocyte filtration of cellular blood products with CMV seronegative blood product selection to support allogenic bone marrow transplant recipients. Allogenic bone marrow transplant recipients are a particular group at high risk for complications from CMV disease. In the primary study, they found no difference in the probability of CMV infection or CMV disease or survival between the bedside-filtered group and the seronegative group. However, in a secondary analysis performed on all infections occurring in the first 100 days of transplantation, it was noted that the probability of CMV disease was greater in the bedside-filtered group than in the seronegative group. Nonetheless, CMV infection and CMV disease rates between the groups did not exceed the prestudy defined difference of 5%. The data from this study suggest that neither approach can be deemed superior.

Subsequent reviews,[15] meta-analysis,[16] and single-center and retrospective studies[17–19] reported variant conclusions on the question. As a guide to understand potential sources of interpretation conflicts, it is important to view each study in the context of the date range of observations and to appreciate that early studies were performed when CMV preventive strategies involved more limited pharmacological and laboratory testing and less sophisticated filter technology. As pointed out by Strauss in a 2016 *Transfusion* editorial, "Despite the resounding success/efficacy of modern leukocyte reduction and the fact that this technology has never been found to be inferior to any other method of preventing transfusion-transmitted CMV, a potential problem does exist during the onset of primary infection."[20] Specifically, Strauss was referring to the inability of leukocyte reduction to eliminate "free virions." However, the editorial conceded this risk to be exceedingly small. Moreover, because it is sometimes suggested that blood products be both seronegative and leukocyte reduced, Strauss commented that "a three-arm randomized clinical trial comparing efficacy of leukocyte-reduction alone vs. CMV sero/antibody-negative blood products alone vs. the 'belt and suspenders' combined approach probably will never be done."[20] This is in part a function of that fact that the differences in CMV reduction potential between the various approaches is so small that the clinical trial would have to be enormous to find any differences between the various approaches. The editorial concluded with a note added in proof: "Leukocyte-reduction alone is the recommended method to prevent TT-CMV—despite the lack of definitive randomized clinical trials."[20] This opinion, published in 2016, reflects the improvement of filtration technology and the results of several more current studies, such as one by Delaney et al[21] that failed to identify any cases of TT-CMV regardless of the CMV risk-reduction method used.

Finally, a series of international consensus guidelines from several organizations on the management of CMV in SOT are available to transplant programs and physicians. Each consensus guideline mentions blood product strategy. In 2010, the International Society of Heart and Lung Transplantation stated, "Blood products should be leukocyte-depleted. Blood products should be cytomegalovirus (CMV) negative if donor and recipient are CMV negative."[22] Therefore, this guideline endorsed using leukocyte-reduced blood products in all circumstances. It then added that blood products for D−/R− patients should specifically be CMV seronegative. In 2013, guidelines from the Transplantation Society International CMV Consensus Group stated, "The use of leukodepleted or CMV seronegative blood products is recommended for these recipients to decrease the risk of transfusion transmitted CMV (strong, moderate)."[23] No separate recommendation was made for using seronegative blood products for a specific donor-recipient pairing. Finally, in 2018, the Transplantation Society International CMV Consensus Group reaffirmed its 2013 position: "To avoid transfusion-transmitted CMV, we recommend the use of leukoreduced or CMV seronegative blood products (strong, moderate)."[24] Of interest is an additional comment in the massive blood transfusion section: "Additional clinical benefit of combining these 2 strategies is not available."[24] To help guide this opinion, the consensus group referenced the 2016 AABB committee report.[25] Therefore, this consensus group not only affirmed the clinical equivalence of CMV safety by either leukocyte reduction or donor serological testing but further implied that there is no advantage to combining CMV reduction strategies.

BLOOD PRODUCT LABELING

Lastly, US blood product labeling conventions may partly explain misunderstanding regarding CMV disease transmission potential. The FDA strictly regulates donated blood products and enforces standardized labeling.[26] Although testing for CMV antibodies is not required, the results of such testing of blood products using an FDA-approved serological method must be affixed with a label declaring the results in a standardized manner.[27] The label may be affixed to the blood product directly or with a tie tag. In terms of serological testing, the typical descriptors are *negative for antibodies to CMV* or *anti-CMV neg*. The term *CMV safe* is not used, because this verbiage would create the potential for a false claim. The unit can be labeled only with test results. No further claim is allowable. Leukocyte-reduced units also can make no CMV safety claim. The words *leukocyte reduced* are incorporated into the blood product label. Interestingly, the Circular of Information for the Use of Human Blood and Blood Components, which is prepared by the AABB, American Red Cross, America's Blood Centers, and the Armed Services Blood Program and acknowledged as an extension of the blood label, states, "Leukocyte-reduced components are considered an alternative to CMV seronegative transfusion."[28] Hence, in an indirect manner, the circular suggests equivalence between leukocyte reduction and serological testing in regard to CMV risk. Though a blood product label that stated "product considered CMV safe by leukocyte reduction method or serological testing method" may aid understanding, this approach is not currently possible because it would create the potential for a false claim. Nonetheless, the evidence suggests that both methods approximate equivalence.

CONCLUSION

In an era of antiviral prevention, early treatment, and universal leukocyte reduction of blood products, the potential in the SOT setting for TT-CMV infection to result in disease is very low. The primary driver for development of new CMV disease in an SOT recipient is receiving an organ from a CMV positive donor. Current consensus guidelines state that either TT-CMV risk reduction by selection of CMV serologically negative donors or universal leukocyte reduction is acceptable for SOT patients. Both approaches yield CMV safe units. Typically, blood units that are universally leukocyte reduced are readily available in most inventories of hospital transfusion services. In the future, direct viral testing of blood donor units and, once available for routine use, universal pathogen inactivation will likely supersede the current practices of serology and leukocyte reduction and render this conundrum to historic interest.

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